A substitute SEQUENCE LISTING is filed herewith. The contents of the paper version of the substitute SEQUENCE LISTING and the computer readable form thereof are the same. It is further submitted that the paper copy of the substitute SEQUENCE LISTING and the computer readable form of the substitute SEQUENCE LISTING do not represent new matter.

The 35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner rejected claims 5, 24 and 26-31 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. This rejection, insofar as it may be maintained with respect to the pending claims, is respectfully traversed.

With respect to claims 24 and 27, the Examiner asserts that it is unclear whether the fragment is a fragment of the extracellular domain (ECD) or of SEQ ID NO:2. The amendments to claims 24 and 27 render this rejection moot.

The Examiner also asserts that claims 5, 24 and 26-30 are indefinite because it is unclear what besides a fragment of SEQ ID NO:2 must be present in the protein or soluble polypeptide. Claims 5 and 27-29 are directed to a soluble H4-1BB protein produced by introducing into a host cell an expression vector encoding SEQ ID NO:2 or a soluble fragment thereof, e.g., the extracellular domain of SEQ ID NO:2 and recovering the recombinant protein from the host cell, e.g., from the culture supernatant. Claims 24, 26 and 30 directed to a purified soluble H4-1BB comprising the extracellular domain of SEQ ID NO:2 or a fragment of the extracellular domain.

If the scope of the subject matter encompassed by the claims is clear and if Applicant has not otherwise indicated that he intends the claims to be of a different scope, the claims satisfy the requirements of § 112(2). In re Borokowski et al., 422 F.2d 904, 164 U.S.P.Q. 642 (C.C.P.A. 1970). Breadth alone is not indefiniteness. In re Gardner, 427 F.2d 786, 166 U.S.P.Q. 138 (C.C.P.A. 1970). Hence, it is clear that Applicant's invention is directed to a portion of H4-1BB having SEQ ID NO:2 which is soluble.

Assuming, for the sake of argument, that the metes and bounds of claims 5, 24 and 26-30 were not readily recognizable to the art worker, at pages 5-6 and 16 of Applicant's specification,

it is disclosed that a fusion protein comprising the extracellular domain of H4-1BB was prepared, and that such a protein can bind to ligands of H4-1BB and be detected by relative activity assays. Moreover, claim 7, as filed, is directed to fragments of SEQ ID NO:2 that are useful to 1) identify ligands of the H4-1BB, 2) stimulate the proliferation of B cells having a H4-1BB ligand, or 3) block H4-1BB ligand binding.

Therefore, the metes and bounds of claims 5, 24, and 26-30 would be readily recognizable and understood by the art worker in the absence of Applicant's specification or, in the alternative, recognized and understood by the art worker in possession of Applicant's specification.

With respect to the rejection of claims 28 and 30, the Examiner alleges that these claims are indefinite because it is not clear under what conditions hybridization may occur. Claims 28 and 30 are directed to a soluble H4-1BB which comprises the extracellular domain of SEQ ID NO:2, or a fragment of the extracellular domain, wherein the DNA which encodes soluble H4-1BB specifically hybridizes to SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, or a combination thereof. The specification at pages 15-16 describes the use of primers, e.g., SEQ ID Nos:3-6 and SEQ ID Nos:7-8, to amplify all or a portion of the DNA which encodes the extracellular domain of SEQ ID NO:2. Thus, it is clear that the invention includes soluble H4-1BB polypeptides encoded by DNA molecules that specifically hybridize to SEQ ID Nos:3-8. Thus, the art worker in possession of Applicant's specification would readily understand and recognize the metes and bounds of claims 28 and 30.

It is respectfully submitted that the pending claims are in conformance with 35 U.S.C. § 112, second paragraph. Therefore, withdrawal of the rejections of the claims under § 112, second paragraph, is respectfully requested.

The 35 U.S.C.§ 112, First Paragraph, Rejection

The Examiner rejected claim 26 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

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Specifically, the Examiner asserts that (a) the specification provides no dosage, toxicity, stability, half-life, or solubility information, (b) the specification does not provide a reasonable expectation that the formulations would treat a disease or clinical condition, e.g., which autoimmune diseases are to be treated, or (c) the use of H4-1BB is unpredictable because the specification fails to provide guidance on how to select enhancing versus suppressing activity, and so it would require undue experimentation to use the claimed invention. As this rejection may be maintained with respect to pending claim 26, it is respectfully traversed.

The Examiner indicates that deletion of the term "pharmaceutical" in claim 26 would not raise the points at issue. Claim 26, as amended, is dependent on claim 24 and is directed to a composition comprising a soluble H4-1BB polypeptide which comprises the extracellular domain of SEQ ID NO:2, or a fragment of the extracellular domain, in admixture with a suitable diluent, carrier or excipient. Hence, the amendments to claim 26 moot the § 112(1) rejection of claim 26. However, it is Applicant's position that amended claim 26 encompasses all compositions, i.e., pharmaceutical compositions as well as non-pharmaceutical compositions.

Therefore, it is respectfully submitted that the pending claims are in conformance with the requirements of 35 U.S.C. § 112, first paragraph. Hence, the Examiner is requested to withdraw the § 112(1) rejection of claim 26.

The 35 U.S.C. § 102(e) Rejection

The Examiner rejected claims 5, 24, 26-28, and 30 under 35 U.S.C. § 102(e) as being anticipated by Goodwin et al. (U.S. Patent No. 5,674,704). The Goodwin et al. patent is available as a reference under 35 U.S.C. § 102(e) as of its filing date, May 6, 1994. However, the Goodwin et al. patent claims the benefit of the filing date of U.S. application Serial No. 08/060,843, filed May 7, 1993. The '843 application discloses a human 4-1BB amino acid sequence (SEQ ID NO:8 in the '843 application) which is identical to Applicant's SEQ ID NO:2. The '843 application also discloses methods to express and purify soluble polypeptides derived from the extracellular domain of human 4-1BB, e.g., amino acids 1-163 of SEQ ID NO:8

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(residues 1-163 of SEQ ID NO:8 do not include the signal sequence of H4-1BB), polypeptides which are envisioned to bind to a ligand termed 4-1BB-L.

In addition, the '843 application describes a soluble fusion protein comprising the extracellular domain of 4-1BB fused to a second polypeptide. The second polypeptide is added for purposes such as facilitating purification or effecting dimer formation. Exemplified second polypeptides are disclosed as the antigenic identification peptides mentioned in U.S. Patent No. 5,011,912, e.g., a peptide having multiple anionic amino acid residues such as DYKDDDDK, and the Fc region of an antibody. Example 3 describes the preparation of a human 4-1BB/Fc fusion protein that encodes amino acids -23 to 163 of SEQ ID NO:8 (i.e., it has the N-terminal 186 amino acids of human 4-1BB including the signal sequence).

To overcome the Goodwin et al. patent as a reference, Applicant's Representatives submitted a Rule 131 Declaration with the Amendment filed on October 26, 1998, and a Supplemental Rule 131 Declaration with the Rule 116 Amendment filed on February 26, 1999. The Examiner asserts that these Declarations are insufficient to overcome the Goodwin et al. patent and Schwarz et al. (a reference cited against the claims under 35 U.S.C. § 103).

The Examiner is respectfully requested to reconsider these Declarations in view of a copy of a Supplemental Rule 131 Declaration executed by Dr. Byoung Kwon, the inventor of the present application, which Declaration was filed in copending application Serial No. 08/948,764 on January 12, 2000 (enclosed herewith). The undersigned attorney for Applicant avers that this is a true copy of the Declaration filed in the '764 application. In the Supplemental Rule 131 Declaration filed on January 12, 2000 in the '764 application, Applicant declares and documents that in the United States, he had prepared a DNA encoding a fusion protein comprising the extracellular domain of H4-1BB prior to the May 7, 1993 effective date of Goodwin et al. In particular, Applicant refers to Exhibit A, attached to and incorporated by reference into the Declaration, as factual evidence of the reduction to practice of the invention prior to the effective date of Goodwin et al.

Applicant states that Exhibit A is a photocopy of certain pages of a laboratory notebook from Applicant's laboratory. The 5' portion of the H4-1BB cDNA, including nucleic acid

sequences encoding the signal peptide and the entire extracellular domain, was amplified by a polymerase chain reaction (PCR) with two primers termed 5' and 3'. The 5' primer included a BglII site at the 5' end of the primer, and the 3' primer included a HindIII site at the 5' end of the 3' primer, to facilitate directional and positional cloning into a mammalian expression vector, APtag-1, that had been digested with BglII and HindIII. The sequence of the 5' primer was: 5' ATAGATCTATGGGAAACAGCTGTTAC 3', and the sequence of the 3' primer was: 5' ATAAGCTTCGGAGAGTGTCCTGGCTC 3'. The introduction and ligation of the BglII-HindIII digested H4-1BB fragment into BglII-HindIII digested APtag-1 results in the introduction of a portion of the coding sequence of H4-1BB upstream of the coding sequence for human placental alkaline phosphatase (AP).

In the Declaration, Applicant indicates that sheet 1 of Exhibit A has the reaction conditions employed to digest the amplified H4-1BB product with BglII and HindIII and to digest APtag-1 with those same enzymes. A portion of the products from these reactions were subjected to agarose gel electrophoresis. Sheet 2 of Exhibit A shows a photograph of that gel. The lane closest to the top of the sheet has the product(s) from the digestion of APtag-1 with HindIII and BglII while the lane beneath that lane has the product(s) from the digestion of the amplified H4-1BB product with HindIII and BglII.

To prepare an expression vector comprising DNA encoding a fusion protein comprising an N-terminal portion of H4-1BB and AP, Applicant states that the products shown on the gel were ligated. The ligation reaction mixture is described on sheet 3 of Exhibit A.

Applicant also states that in order to prepare a fusion protein in which a portion of H4-1BB was linked in frame to AP, it is logical to conclude that the nucleotide sequence of H4-1BB was known. In particular, the amplification of a particular portion of the nucleic acid sequence of H4-1BB with primers, the selection of restriction enzymes that do not cleave H4-1BB DNA in the portion of the H4-1BB DNA to be inserted into an expression vector, and the introduction of the digested H4-1BB DNA so that the coding sequence is linked in frame with the coding sequence of another protein, shows that Applicant was in possession of the nucleotide sequence of H4-1BB.

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Claims 5, 24, 26-28, and 30 are directed to a soluble H4-1BB polypeptide, e.g., a polypeptide which comprises at least a portion of the extracellular domain of SEQ ID NO:2. Thus, Exhibit A evidences that Applicant was in possession of the sequence of H4-1BB. Moreover, Exhibit A demonstrates that the invention claimed in the present application was reduced to practice prior to the effective date of Goodwin et al., i.e., May 7, 1993.

The Examiner is reminded that Applicant need demonstrate only so much of the claimed invention as taught by the prior art reference, or what is rendered obvious in view of the reference. In re Stempel, 113 U.S.P.Q. 77 (C.C.P.A. 1957); In re Spiller, 182 U.S.P.Q. 614 (C.C.P.A. 1974). Thus, the enclosed Rule 131 Declaration alone, or in combination with the earlier-filed Rule 131 Declarations, properly establishes Applicant's date of invention as earlier than the effective date of Goodwin et al.

Therefore, Goodwin et al. cannot be used to support a rejection of the claims under 35 U.S.C. § 102(e), and so the Examiner is respectfully requested to withdraw the § 102(e) rejection of the claims.

The 35 U.S.C. § 102(a) Rejection

The Examiner rejected claims 5, 24 and 26-31 under 35 U.S.C. § 102(a) as being anticipated by Alderson et al. (Eur. J. Immunol., 24, 2219 (1994)). The present application is a continuation of U.S. application Serial No. 08/461,652, filed on June 5, 1995, which is a division of U.S. application of Serial No. 08/122,976, filed on September 16, 1993. Thus, the effective date of the present claims is earlier than the effective date of Alderson et al., which appears in a 1994 volume of the European Journal of Immunology. Hence, Alderson et al. is not prior art to the pending claims. Thus, the Examiner is requested to withdraw the § 102(a) rejection of the claims.

The 35 U.S.C.§ 103 Rejections

The Examiner rejected claims 5, 24, 26-28, and 30 under 35 U.S.C. § 103(a) as being unpatentable over Schwarz et al. (GenBank Accession No: L12964), Pollock et al. (J. Immunol.,

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150, 771 (1993)), and Chalupny et al. (Proc. Natl. Acad. Sci. USA, 89, 10360 (1992)). The Examiner also rejected claims 5-6, 24 and 26-31 under 35 U.S.C. § 103(a) as being unpatentable over Alderson et al. and Kim et al. (J. Immunol., 151, 1255 (1993)). These rejections are respectfully traversed.

Schwarz et al. disclose the nucleotide sequence encoding, and the inferred amino acid sequence of, ILA. The inferred amino acid sequence of ILA has one amino acid substitution relative to Applicant's SEQ ID NO:2. The substitution is at amino acid position 107.

Schwarz et al. is available as a reference under 35 U.S.C. § 102(a) as of its publication date, April 22, 1993. In the Supplemental Rule 131 Declaration discussed above, Applicant states that prior to April 22, 1993, in the United States, he prepared a DNA encoding a fusion protein comprising a portion of H4-1BB. Since Applicant need demonstrate only so much of the claimed invention as is taught by, or rendered obvious by, the prior art reference, it is respectfully submitted that Schwarz et al. is not available as prior art against the pending claims. In re Stempel, 113 U.S.P.Q. 77 (C.C.P.A. 1957); In re Spiller, 182 U.S.P.Q. 614 (C.C.P.A. 1974). Therefore, the enclosed Supplemental Rule 131 Declaration alone, or in combination with the previously filed Rule 131 Declarations, properly establishes Applicant's date of invention as earlier than the publication date of Schwarz et al. Hence, Schwarz et al. is not available as a reference against the pending claims under 35 U.S.C. § 102(a)/§ 103(a).

Even if, assuming for the sake of argument, Schwarz et al. is available as a reference against the present claims, Schwarz et al. do not disclose or suggest preparing an expression vector with their disclosed cDNA, much less which portion, if any, of the polypeptide encoded by the ILA cDNA is extracellular.

Pollock et al. disclose that a vector was used to express recombinant, soluble murine 4-1BB and full-length murine 4-1BB in *Sf*21 insect cells. Immunoblot analysis of 4-1BB proteins in insect cell lysates was accomplished with a primary antibody to murine 4-1BB and a secondary antibody, which was either anti-rabbit IgG or anti-rat IgG, that had been conjugated to alkaline phosphatase (page 773). The authors also note that they are using a murine 4-1BB/ alkaline phosphatase fusion protein to identify cell surface ligands that bind to murine 4-1BB (page 779).

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Nevertheless, Pollock et al. do not disclose or suggest isolating the human 4-1BB gene, or the preparation or purification of a protein encoding at least a portion of human 4-1BB. Therefore, Pollock et al. do not render Applicant's invention obvious.

Chalupny et al. relate to the preparation of a murine 4-1BB/immunoglobulin fusion (murine 4-1BB/Ig) protein which lacks the murine 4-1BB signal peptide, and its use in immunohistochemistry studies to identify tissues that express 4-1BB ligand. The authors also report the recombinant expression of murine 4-1BB in COS cells. However, there is nothing in this reference which suggests the isolation of the human homolog of murine 4-1BB, or the preparation of a recombinant protein having human 4-1BB or a portion thereof. Therefore, this reference does not render Applicant's invention obvious.

With respect to the rejection of claims 5-6, 24 and 26-31 over Alderson et al. and Kim et al., as noted above, Alderson et al. is not § 102(a) prior art to the present application and so cannot form the basis for a rejection under § 103(a).

Kim et al. relate that in murine T cells, murine 4-1BB physically associates with murine $p56^{lck}$ and that this association also occurs in insect cells and HeLa cells which express recombinant murine 4-1BB and $p56^{lck}$. Murine 4-1BB was detected by a monoclonal antibody raised to a recombinant soluble murine 4-1BB protein (citing to Pollock et al.) or rabbit anti-4-1BB antisera raised to amino acid residues 82-92 of murine 4-1BB. Kim et al. do not teach or suggest a soluble form of the human homolog of murine 4-1BB. Hence, Kim et al. do not render Applicant's invention obvious.

The Examiner asserts that it would have been obvious to express the full-length or the extracellular domain of the human polypeptide encoded by the cDNA of Schwarz et al. by substituting the full-length cDNA of Schwarz et al. or a portion thereof which corresponds to the extracellular domain of the murine 4-1BB cDNA disclosed by Pollock et al. or Chalupny et al. to produce a soluble H4-1BB polypeptide. The Examiner also asserts that it would have been obvious to substitute the full-length DNA of Alderson et al. for the full-length 4-1BB DNA of Kim et al. and express the encoded protein as taught by Kim et al. and purify the protein using the antibody disclosed in Alderson et al.

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However, to support a *prima facie* case of obviousness, there must be a suggestion or teaching that Applicant's invention could or should be prepared and a reasonable expectation of success in the prior art. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991); In re O'Farrell, 853 F.2d 894, 7 U.S.P.Q.2d 1673 (C.A.F.C. 1988). None of the available cited references, i.e., Pollock et al., Chalupny et al., and Kim et al., alone or in combination, disclose or suggest Applicant's invention as none of the available references discloses or suggests the isolation of the human homolog of murine 4-1BB, much less the preparation of a soluble protein comprising at least a portion of the extracellular domain of the human homolog.

Moreover, even if it were obvious to try to isolate the human homolog of murine 4-1BB and to prepare a fusion protein comprising a portion of the human homolog, "obvious to try" is an impermissible standard to use in an obviousness determination. In re Antonie, 559 F.2d 618, 195 U.S.P.Q. 6 (C.C.P.A. 1977); In re Tomlinson et al., 363 F.2d 928, 150 U.S.P.Q. 623 (C.C.P.A. 1966).

Further, with respect to claims 5-6, 24, and 26-31, a *prima facie* case of obviousness can only be established if the prior art suggests to one of ordinary skill in the art to make the substitution or modification necessary to convert a prior art compound into the claimed compound. In re Taborsky, 502 F.2d 775, 183 U.S.P.Q. 50 (C.C.P.A. 1974). The Examiner is reminded that the surprising divergence between the amino acid sequence of murine and human 4-1BB is not provided by the limited and specific disclosures of the available cited art. Moreover, although certain murine 4-1BB fusion and/or soluble proteins are disclosed in the prior art, Applicant's soluble human protein is not a structurally analogous protein to the disclosed murine fusion and/or soluble proteins, as the mouse and human 4-1BB proteins have only 65% homology to each other. Since SEQ ID NO:2 is not closely structurally related to the inferred amino acid sequence of murine 4-1BB, and since the Examiner has not provided an explanation of how the prior art would suggest the modifications necessary to arrive at Applicant's soluble H4-1BB protein from the disclosures of the available prior art structure, a *prima facie* case of obviousness has not been made out.

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In re Deuel, 51 F.3d 1552, 34 U.S.P.Q.2d 1210 (Fed. Cir. 1995) further compels a conclusion of nonobviousness with respect to claims which recite a specific sequence identifying number, i.e., SEQ ID NO:2. In Deuel, the Court held that, with respect to claims directed to DNA segments of defined sequence, the fact that methods for obtaining the DNA were available, even in combination with the existence of a motivation to isolate the claimed DNA, was irrelevant to the question of obviousness of the DNA. In order to find the DNA segment obvious, an examiner is required to demonstrate structural obviousness of the DNA segment apart from the existence of a method which is available for its preparation:

> The PTO's focus on known methods for potentially isolating the claimed DNA molecules is also misplaced because the claims at issue define compounds, not methods. See In re Bell, 991 F.2d 781, 785, 26 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1993). In Bell, the PTO asserted a rejection based upon the combination of a primary reference disclosing a protein (and its complete amino acid sequence) with a secondary reference describing a general method of gene cloning. We reversed the rejection, holding in part that "[t]he PTO's focus on Bell's method is misplaced. Bell does not claim a method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they are made." Id. . . . Thus, even if, as the examiner stated, the existence of general cloning techniques, coupled with knowledge of a proteins' structure, might have provided motivation to prepare a cDNA or made it obvious to prepare a cDNA, that does not necessarily make obvious a particular claimed cDNA. "Obvious to try" has long been held not to constitute obviousness. In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988). (emphasis in original)

34 U.S.P.Q.2d at 1215-16.

It is submitted that the Examiner has failed to meet the burden set by Deuel and its predecessors, such as In re Bell (991 F.2d 781, 785, 26 U.S.P.Q.2d 1529 (Fed. Cir. 1993), to make out and support a case for structural obviousness of the claimed soluble proteins. In view of the fact that the Examiner has not compared the structural features recited by claims 5,-6, 24, and 26-31, i.e., a soluble H4-1BB protein, e.g., comprising the extracellular domain of SEQ ID NO:2, to the structural features of the amino acid sequence of murine 4-1BB alleged to be

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present in the prior art, it is respectfully submitted that the Examiner has not made out a *prima facie* case of obviousness.

Based on the discussion above, the Examiner is respectfully requested to withdraw the § 103(a) rejections of the claims.

Conclusion

Applicant believes the claims are in condition for allowance and request reconsideration of the application and allowance of the claims. The Examiner is invited to telephone the below-signed attorney at (612) 373-6959 to discuss any questions which may remain with respect to the present application.

Respectfully submitted,

By Applicant's Representatives,

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Date January 24, 2000 By _____
Janet E. Embretson
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on this 24 day of January, 2000.

Dawn M. Poole
Name

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Signature